REMARKS

I. Claim Rejections-35 U.S.C. § 112, Second Paragraph

Claims 6-8 and 21-23 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite or failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

The Examiner states the "recombinant immunoglobulin" recited in claims 6-7 and 21-22 has no antecedent basis in claims 1 and 16 respectively. Base claims 1 and 6 only recite an immunomodulating amount of immunoglobulin.

Applicants have amended claims to provide proper antecedent basis, thus alleviating this rejection.

The Examiner states claims 8 and 23 are indefinite for being in improper Markush format. The Examiner recommends use of the phrase "selected from the group consisting of..." with the use of the conjunction "and" rather than "or" in listing the species.

Applicants have amended claim 5 by using the conjunction --and-- rather than "or", thus alleviating this rejection.

II. Claim Rejections-35 U.S.C. § 112, First Paragraph

Claims 1-8 and 16-23 were rejected under 35 U.S.C. § 112, first paragraph, because the specification while being enabling for a method for treating an animal suffering from chronic fatigue syndrome associated with altered levels of IgG comprising administering to said animal immunoglobulin derived from blood, egg, milk, recombinant immunoglobulin expressed in a plant and recombinant immunoglobulin expressed in a bacteria does not reasonably provide enablement for a method for treating an animal suffering from any immune dysfunction disease state associated with altered levels of IgG comprising administering to said animal an

immunomodulating amount of immunoglobulin from an animal source in claims 1 and 16. The Examiner states the specification does not enable any person skilled in the art to which it pertains or with which it is most clearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants have amended the claims to show that immune dysfunction disease states are those which are characterized by chronic immune stimulation (see spec. page 11, lines 13-16). Moreover, the specification teaches that those skilled in the medical arts will readily appreciate that the doses and schedules of the immunoglobulin will vary depending on the age, health, sex, size, and weight of the patient rather than administration, etc. (See spec. page 8, 4th para.). These parameters can be determined for each system by well-established procedures and analysis. (Id.) It has been shown that chronic fatigue syndrome, for example, resembles other disorders, including multiple sclerosis and lupus. Thus, one of ordinary skill would be enabled by the specification.

III. Claim Rejections-35 U.S.C. § 102

Claims 1-2, 8, 16-17, and 23 were rejected under 35 U.S.C. § 102(b) as being anticipated by Lloyd et al. (Am J Med..1990, 89:561-568) as is evidenced by INTRAGAM® Data Sheet.

The Examiner states Lloyd teaches a method of treating patients suffering from chronic fatigue syndrome characterized by IgG subclass deficiency comprising administering to the patients, an immunomodulating amount of immunoglobulin (INTRAGAM®) from an animal source. The Examiner further states Lloyd teaches that immunoglobulin is administered by continuous infusion in a dosage of 2g (IgG)/kg or placebo (10% w/v maltose).

Claims 1 and 16 have been amended to recite that the administration is oral. As stated by the Examiner, Lloyd teaches that teaches that immunoglobulin is administered by infusion.

Claims 2 and 8 are dependent on amended claim 1, and by virtue of their dependency contains all the limitations of independent claim 1. Claims 17 and 23 are dependent on claim 16, which has been amended, and by virtue of their dependency contains all the limitations of independent claim 16. Support for the amendment is found in the specification at page 3, line 35 to page 4, line 2 and at page 5, lines 22-23.

IV. Claim Rejections-35 U.S.C. § 103

Applicants submit that the subject matter of the various claims was commonly known at the time any invention covered herein was made. Applicants acknowledge their obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 1, 3-4, 16 and 18-19 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lloyd et al. (Am J Med: 1990, 89:561-568), as is evidenced by INTRAGAM® Data Sheet, in view of U.S. Patent No. 5,871,731 ('731).

The Examiner states the '731 patent teaches the immunoglobulins can be prepared by known techniques from plasma, for example from eggs or from milk. Furthermore, the isolation of immunoglobulins from milk of immunized cows or from eggs from immunized hens is used to immunize pregnant women or mother animals against bacterial pathogens. The '731 patent further teaches that the production of the immunoglobulins from plasma is relatively complicated and therefore very expensive, the immunoglobulins are preferably isolated from milk.

The Examiner states it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the immunoglobulin from egg or from milk taught by

the 731 patent with immunoglobulin from blood in a method of treating the animal suffering from chronic fatigue syndrome taught by Lloyd et al.

In addition, the Examiner asserts one of ordinary skill in the art at the time the invention was made would have been motivated to do so because producing immunoglobulin from milk is easy and inexpensive and producing immunoglobulins from milk of immunized cows or from eggs from immunized hens is used to immunize pregnant women or mother animals against bacterial pathogens as taught by the 731 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicants traverse this rejection. There is no suggestion in the cited references that they be combined in the manner proposed by the Examiner. Absent such a suggestion, a person skilled in the art who was looking for a solution to the problem of treating patients with chronic fatigue syndrome (CFS) characterized by IgG subclass deficiency by administering an immunoglobulin from an animal source via intravenous infusion at high doses, as exhibited by Lloyd would hardly be disposed on any objective basis to consider a reference like 731, which is not only unconcerned with CFS and intravenous administration of an immunoglobulin, but which teaches, that since the production of immunoglobulins from plasma is relatively complicated and very expensive, the immunoglobulins are most preferably from colostral milk.

Applicants submit Lloyd teaches a method of treating chronic fatigue syndrome with immunoglobulins via intravenous administration as evidenced by the INTRAGAM® Data Sheet, which teaches the immunoglobulin is intended for intravenous administration. (See

INTRAGAM® Data Sheet, pg. 1, par. 2). In fact, the Data Sheet discloses in "Warnings and Precautions" that INTRAGAM® should only be administered intravenously. (See INTRAGAM® Data Sheet, pg. 2, under "Warnings and Precautions"). Moreover, INTRAGRAM® is made from human plasma. Lloyd does not suggest or teach using an immunoglobulin derived from milk or egg as evidenced by reference to the INTRAGAM® Data Sheet.

U.S. Patent '731 teaches treatment of chronic pain syndrome, not chronic fatigue syndrome where the immunoglobulin is isolated from milk.

Moreover, the specification teaches that with oral administration of antibody, one can use a different specie source, without the threat of allergic reaction. This opens the door to milk, colostrum, serum, plasma, eggs, for example, from pigs, sheep, goats, cattle, etc. as the means of producing immunoglobulins, but large amounts of immunoglobulin that would be required for sustained treatment. (See spec. pg. 12, lines 7-13). Thus Applicant's invention differs from US Patent '731 because there is no need for preimmunization. Thus, one skilled in the art would not likely use such a reference alone or in combination with another reference in an attempt to solve such a problem.

Moreover, Applicants disclose that the method used in their invention is in fact workable and Applicants have overcome what '731 views as an insuperable barrier. US Patent '731 teaches that the production of the immunoglobulins from plasma is relatively complicated and therefore very expensive. (See col. 2, lines 65-67). A disclosure in the prior art that discourages the making of the claimed invention undermines prima facia obviousness and suggests the inventions' unobviousness. (See generally In re Sponnoble, 405 F.2d 578, 587 (C.C.P.A. 1969); In re Caldwell, 319 F.2d 254, 256 (C.C.P.A. 1963)). Clearly, '731 discourage embodiments of Applicants' claimed invention. For example, Applicants disclose on page 12 of the specification

that "prior to applicants' invention, one could not produce massive amounts of antibody..." Therefore, the invention as a whole is not obvious to one of skill in the art. Applicants respectfully request the Examiner to withdraw this rejection.

Claims 1, 5-6, 16, and 20-21 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lloyd et al. (Am J Med. 1990, 89:561-568), as is evidenced by INTRAGAM® Data Sheet, in view of WO 96/21012 (1996) (WO '012).

Applicants traverse this rejection. There is no suggestion in the cited references that they be combined in the manner proposed by the Examiner. Absent such a suggestion, a person skilled in the art who was looking for a solution to the problem of treating patients with chronic fatigue syndrome (CFS) characterized by IgG subclass deficiency by administering an immunoglobulin from an animal source via intravenous infusion at high doses, as exhibited by Lloyd, would hardly be disposed on any objective basis to consider a reference like WO '012. WO '012 is not only unconcerned with CFS and intravenous administration of an immunoglobulin, but teaches instead a method of expressing immunoglobulins in plants wherein the transgenic plant assembles the secretory immunoglobulins. The secretory immunoglobulins are composed of alpha, J, and kappa immunoglobulin chains associated with a protection protein derived from pIgR, wherein the protection proteins give the immunoglobulins, which contain them, properties such as resistance to chemical and enzymatic degradation and resistance to denaturation. (See WO '012 page 6, lines 11-14). There is no motivation found in the WO '012 reference whereby a person of ordinary skill would make the combination asserted by the Examiner because the WO '012 publication discloses a method for assembling secretory immunoglobulins, which do not stimulate the complement system but functions by inhibiting microorganisms from binding to the epithelium. One of ordinary skill is apprised in knowing

that the complement system is an array of approximately twenty serum proteins activated by antibodies binding to the pathogens or directly by the pathogen. Secretory IgA also known as secretory immunoglobulin (sigA) functions in external defenses at mucosal surfaces. Therefore, one skilled in the art looking to immunomodulate the serum levels of animals by oral administration of an immunoglobulin expressed in transgenic plants would not look to a reference like the WO '012 publication, because its still a secretory immunoglobulin, only in this case, its being expressed in a plant. Thus, Applicant's invention is patentable in over Lloyd et al. in view of WO '012. Applicants respectfully request Examiner to withdraw this rejection.

Claims 1, 5, 7, 16, 20, and 22 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lloyd et al. as evidenced by INTRAGAM® Data Sheet, in view of U.S. Patent No. 5,348,867 (1994) ('867).

The Examiner states the teachings of Lloyd et al. reference have been discussed, supra.

Additionally, the claimed invention differs from the reference teachings only by the recitation that the animal immunoglobulin is recombinant in claims 5 and 20 wherein the recombinant is expressed in bacteria in claims 7 and 22.

The Examiner states the '867 patent teaches recombinant immunoglobulins from bacteria. The '867 patent further teaches that the variety of recombinant immunoglobulins from bacteria is greater than the number of antibody molecules that can be generated by the mammalian cell (column 2, line 68 and column 3, lines 1-12 in particular).

Applicants traverse this rejection. There is no suggestion in the cited references that they be combined in the manner proposed by the Examiner. Absent such a suggestion, a person skilled in the art who was looking for a solution to the problem of treating patients with chronic fatigue syndrome (CFS) characterized by IgG subclass deficiency by administering an

immunoglobulin from an animal source via intravenous infusion at high doses, as exhibited by Lloyd, would hardly be disposed on any objective basis to consider a reference like US Patent '867, which is not only unconcerned with treating an immune dysfunction disease, but which shows absolutely no recognition of the problem of effective replacement therapy, let alone, using intravenous immunoglobulin to induce serum IgG levels. On the contrary, '867 merely teaches a recombinant DNA vector that promotes transport of a periplasmic or other protein to the external face of the outer membrane of a gram negative bacterial cell in the absence of any specific export components. This is distinguishable from Applicants' claimed invention wherein the immunoglobulin is purified from transgenic bacteria. Therefore, Applicants' claimed invention, as a whole, is not obvious to one of ordinary skill in the art and is therefore, patentable over Lloyd in view of US Patent '867. Applicants respectfully request Examiner to withdraw this rejection.

V. Conclusion

It is believed the application is in condition for allowance. Allowance is respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Reconsideration and allowance is respectfully requested.

Respectfully submitted,

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Application No. 09/973,284

AMENDMENT — VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims

Please amend claim 1, 6, 7, 8, 16, 21, 22, and 23 as follows:

1. (Amended)

A method of treating an animal suffering from [an] a chronic immune dysfunction disease state associated with altered levels of IgG comprising:

administering orally to said animal an immunomodulating amount of immunoglobulin from an animal source.

6. (Amended)

The method of claim 1 wherein said immunoglobulin is a recombinant immunoglobulin [is] expressed in a plant.

7. (Amended)

The method of claim 1 wherein said immunoglobulin is a recombinant immunoglobulin [is] expressed in [a] bacteria.

8. (Amended)

The method of claim 1 wherein said chronic immune dysfunction disease states is selected from the group consisting of:

Kawasaki syndrome, chronic fatigue syndrome, asthma, rheumatoid arthritis, Crohn's disease, [glaforsis] graft-vs-host disease, human immunodeficiency virus, thrombocytopenia, anemia, nuetropenia, hemophilia, myasthenia gravis, multiple sclerosis, systemic lupus, demyelinating polyneuropathy, polymyositis and Sjogren's syndrome, insulin-dependent diabetes mellitus, bullous pemphiguoid, thyroid-related eye disease, ureitis, [or] and any other disease state associated with altered IgG levels.

16. (Amended)

A method of treating a disease state associated with a chronic immune dysfunction in an animal comprising:

administering orally to said animal an immunomodulating amount of immunoglobulin composition, wherein said immunoglobulin is from an animal source.

21. (Amended)

The method of claim 16 wherein said immunoglobulin is a recombinant immunoglobulin [is] expressed in a plant.

22. (Amended)

The method of claim 16 wherein said immunoglobulin is a recombinant immunoglobulin [is] expressed in [a] bacteria.

23. (Amended)

The method of claim 16 wherein said chronic immune dysfunction disease states is selected from the group consisting of:

Kawasaki syndrome, chronic fatigue syndrome, asthma, rheumatoid arthritis, Crohn's disease, [glaforsis] graft-vs-host disease, human immunodeficiency virus, thrombocytopenia, anemia, nuetropenia, hemophilia, myasthenia gravis, multiple sclerosis, systemic lupus, demyelinating polyneuropathy, polymyositis and Sjogren's syndrome, insulin-dependent diabetes mellitus, bullous pemphiguoid, thyroid-related eye disease, uveitis, [or] and any other disease state associated with altered IgG levels.